IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Ashok V. Purandare

Serial No.: 10/648,677 Group Art Unit: 1624

Filed: August 25, 2003 Examiner: M. Berch

For: ANTAGONISTS OF CHEMOKINE RECEPTORS

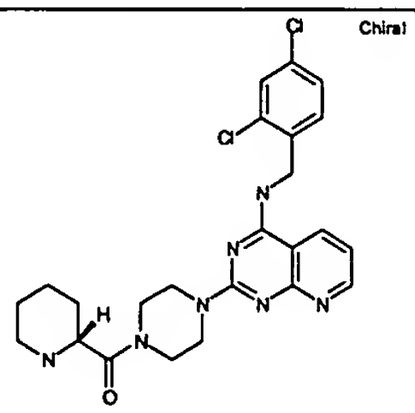
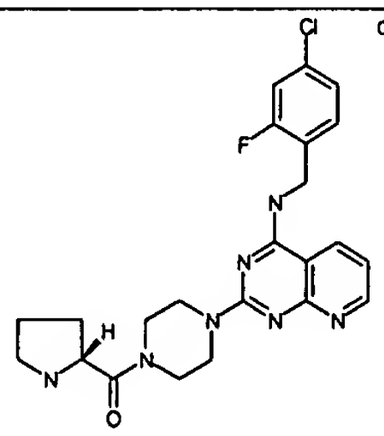
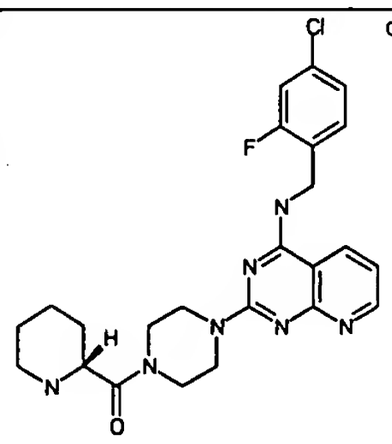
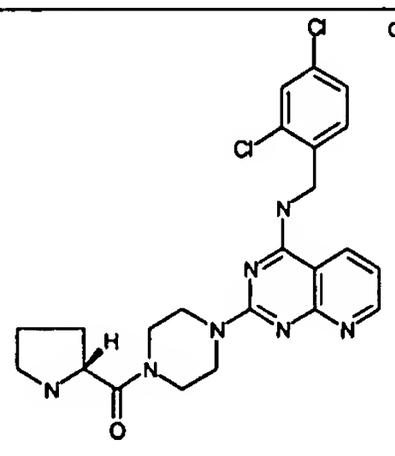
Commissioner for Patents
Alexandria, VA 22313-1450

DECLARATION PURSUANT TO 37 C.F.R. 1.132

I, Dr. John E. Somerville, Jr. , declare and say that:

1. I am a contributor of supportive data for the above-identified patent application.
2. I have been employed by Bristol-Myers Squibb Co. since approximately October 1990, I am currently a Group Leader, and served as a Program Leader for the BMS chemokine receptor CCR4 antagonist program from approximately April 1997 to January 2002.
3. I am familiar with the above-identified patent application.
4. I understand that the Examiner has rejected compound claims 1, 2, 5, and 6 in the above-referenced patent application for lack of enablement contending that "no utility has been demonstrated for the instant compounds".
5. The compounds described by claims 1, 2, 5, and 6 of the above-referenced patent application were identified as potent antagonists of CCR4 as tested in the CEM assay described on pages 46-48 of the above –referenced application. CCR4 and its ligands have attracted significant

attention due to their involvement in mediating various allergic inflammatory conditions such as asthma, acute dermatitis, etc. Compounds of the invention described in claims 1, 2, 5, and 6 of the above-referenced application and their assay activity are reported below.

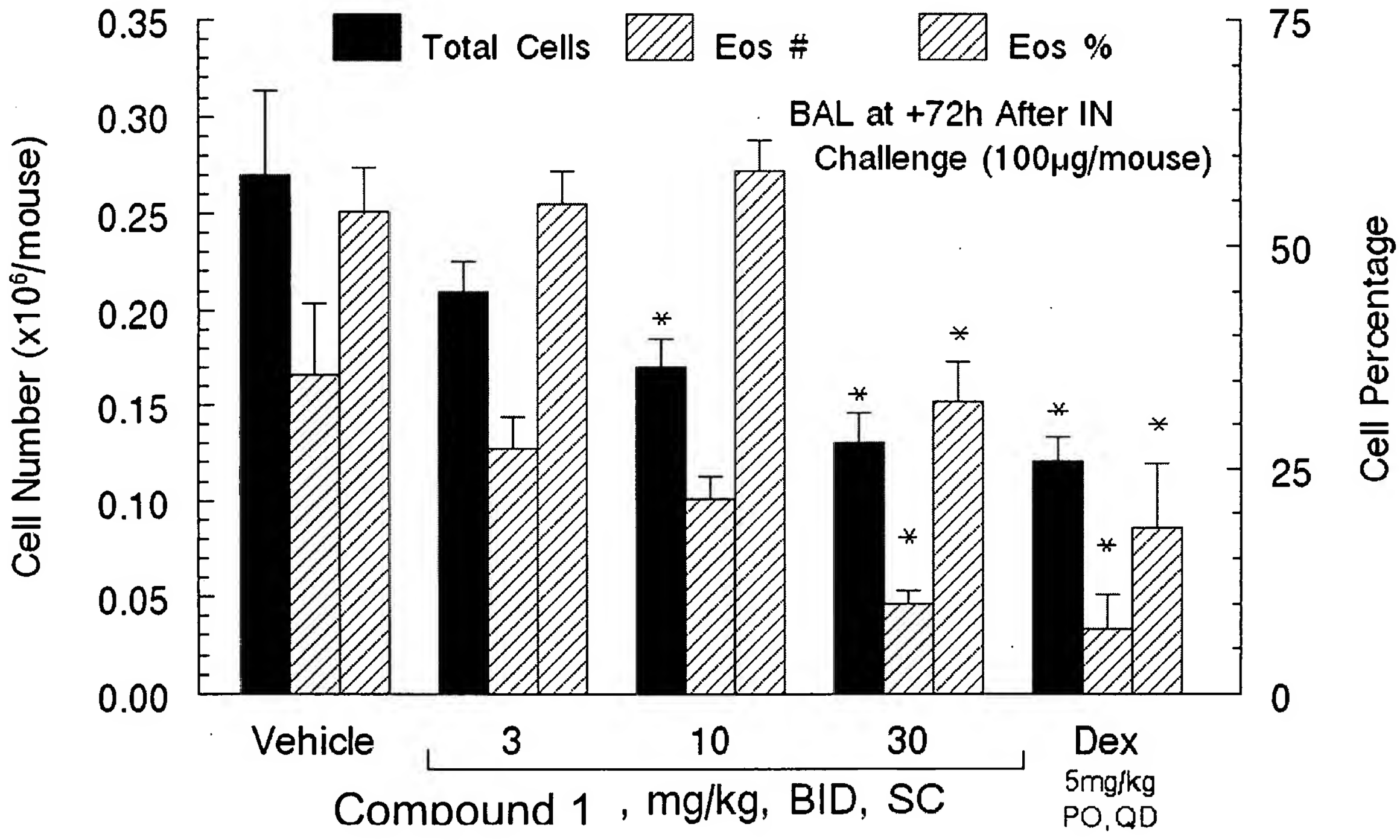
COMPOUND NO.	STRUCTURE	CEM Binding Assay (IC50 in μM)
1		0.290/0.139*
2		0.274
3		0.586
4		0.296

- two trials were conducted on this compound resulting in two IC_{50} values.

The sub-micromolar activities measured for the compounds above were significantly active relative to chemokine antagonists that had been reported in the literature at the time of this study.

6. The effectiveness of the CCR4 inhibitors in treating inflammatory disease was demonstrated in a murine allergic inflammation model that is accepted in the art as a reasonable predictor of human allergic inflammation, particularly asthma, as follows. Compound No. 1 was administered sub-cutaneously twice a day at a 10, 30, and 100 mg/kg dose to mice previously challenged with ovalbumin**. Dexamethasone was administered orally at 5 mg/kg and was used as a control to assess relative efficacy. Evidence of dose-dependent inhibition by compound 1 of eosinophil infiltration into allergic lung airways is reported in the table below. Total leukocytes (solid bars), total eosinophils (hatched bars), and percent eosinophils (open bars) in bronchoalveolar lavage (BAL) fluid were determined as described below**. Compound 1 reduced the recruitment of eosinophils with an IC_{50} of 10 mg/kg. Additionally, at 30 mg/kg, compound 1 was almost as effective as dexamethasone at 5 mg/kg in reducing eosinophilic infiltration into mouse BAL. Accordingly I conclude that the CCR4 inhibiting compounds claimed in the above-identified patent application can reasonably be expected to have effectiveness for the treatment of asthma.

CCR4 Inhibitor Compound 1 in Allergic Eosinophilic Lung Inflammation in Mice



Mean+/-SEM
n=7-8/group

* p<.05 vs Veh
Student's t Test

**BALB/c female mice, 6-8 weeks of age (Harlan, Indianapolis), were immunized intra-peritoneally with 100 µg of ovalbumin (OVA; Sigma) in alum adjuvant (Pierce) and similarly boosted 10 days later. Ten days after the booster, the mice were challenged intra-nasally with 100 µg OVA in 50 ul pyrogen-free saline. Seventy-two hours after challenge, mice were killed by barbiturate overdose and lungs were lavaged via a tracheostomy with 1 ml ice-cold Hanks' balanced salt solution (CA2+ and Mg2+ free) containing 10% fetal bovine serum. Total recovered leukocytes were enumerated by electronic cell counter (Scharfe Ssytem, Reutingen, Germany). Cyto-centrifuge smears (Shandon, Pittsburg) were stained with Wright-Giemsa stain and 200 cells per sample were classified by microscopic differential.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or by imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application, any patent issuing there upon, or any patent to which this verified statement is directed.

Date: 10/13/2006

Dr. John E. Somerville, Jr.